REMARKS

I. CLAIM AMENDMENTS

Claims 1-37 were pending. Claims 1 and 3 have been amended to delete the terms "preventing", "prevention", "prophylactically" and "clathrate or prodrug", and to recite a species of the selective cytokine inhibitory drug. Claims 5-9, 13 and 14 have been amended to correct their dependencies. Claims 2, 4, 10-12 and 15-37 have been canceled without prejudice. Applicant reserves the right to pursue any canceled subject matter in continuation and/or divisional applications. Claims 38-50 have been added. The claims are supported by the specification, *e.g.*, paragraphs [0231], [0233], [0234], [0235], [0239], [0288] to [0291]. No new matter has been added.

Upon entry of these amendments, claims 1, 3, 5-9, 13, 14 and 38-50 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

II. RESPONSE TO ELECTION/RESTRICTION REQUIREMENT

Restriction is required on pages 3-5 of Office Action. In order to fully respond to the requirement, Applicant elects the invention of group I, method claims 1-25 for further prosecution in the this application without traverse. Species elections are required on pages 4-5 of Office Action. Applicant further elects (a) cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide as the cytokine inhibitory drug species; (b) dexamethasone as the second agent; (c) S enantiomer; and (d) a primary myelodysplastic syndrome.

III. REJECTIONS UNDER 35 U.S.C. §112

Claims 1, 3, 4-10 and 13-25 are rejected under 35 U.S.C. §112, first paragraph, because as alleged by the Examiner, the specification, while being enabling for treating myelodysplastic disorders (MDS), does not reasonably provide enablement for preventing myelodysplastic disorders. (Office Action, page 5).

Solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, the claims have been amended to delete the terms "preventing", "prevention" and "prophylactically." Accordingly, the rejection is moot and should be withdrawn.

Further, claims 1-10 and 15-25 are rejected under 35 U.S.C. §112, first paragraph, because, as alleged by the Examiner, the specification, while being enabling for treating myelodysplastic disorders with some selective cytokine inhibitory agents, does not reasonably provide enablement for treating any myelodysplastic syndrome disorder as disclosed with any selective cytokine inhibitory agent. (Office Action, page 9).

Solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, the claims have been amended to recite particular compounds recited in claims 13 and 14 which are not rejected under this 35 U.S.C. §112. Accordingly, the rejection is moot and should be withdrawn.

IV. DOUBLE PATENTING REJECTIONS

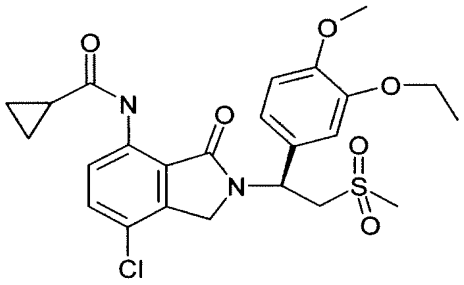
Application No. 11/250,408

Claims 1-10 and 13-25 are provisionally rejected on the ground of nonstatutory double patenting over claims 46-49, 53-54 and 65 of Application No. 11/250,408. In particular, the Examiner states that the claimed subject matter is fully disclosed in the application and would be covered by any patent granted on that application since both applications claim common subject matter (Office Action, page 12). Applicant respectfully disagrees.

Obviousness-type double patenting is a judicially created doctrine intended to prevent improper timewise extension of the patent right by prohibiting the issuance of claims in a second patent which are not "patentably distinct" from the claims of a first patent. *See In re Braat*, 19 U.S.P.Q.2d 1289, 1291-92 (Fed. Cir. 1991). In *General Foods Corp. v. Studiengesellschaft Kohle mbH*, the Federal Circuit further explained that in an obviousness-type double patenting rejection "it is important to bear in mind that comparison can be made only with what invention is *claimed* in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim *defines* and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference." *See, e.g., General Foods Corp.*, 23 U.S.P.Q.2d 1839, 1845 (Fed. Cir. 1992).

Application No. 11/250,408 has matured into the U.S. Patent No. 7,256,210 ("the '210 patent") issued to Man *et al.* on August 14, 2007. Applicant respectfully submits that the Patent Office is mistaken concerning what is claimed in the claims of the '210 patent and by not considering what the claims of the '210 patent define, the Patent Office arrives at a legally improper double patenting rejection.

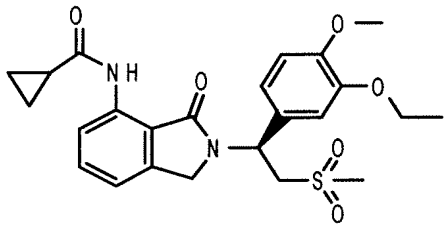
The claims of the '210 patent recite (1S)-cyclopropanecarboxylic acid {**7-chloro**-2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}amide:



,

or a pharmaceutically acceptable salt or solvate thereof; a pharmaceutical composition comprising the compound; or methods of treating atopic dermatitis, Crohn's disease or colon cancer using the compound.

The instant claims recite methods for treating MDS with cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide or a pharmaceutically acceptable salt, solvate, hydrate, or stereoisomer thereof:



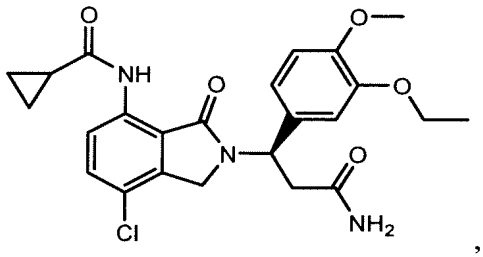
Thus, the instantly recited compound (having no chloro substituent in the isoindoline ring) is different from the compound recited in the '210 patent. Further, the claims of the '210 patent are silent as to the claimed methods of treating MDS. Because the claims of the '210 patent do not disclose or suggest the claimed methods of treating an MDS using the specific compounds, the present claims are not obvious and therefore they are distinct from the claims of the '210 patent. Therefore, rejection of claims 1-10 and 13-25 over the claims of the '210 patent or Application No. 11/250,408 should be withdrawn.

Application No. 11/818,927

Claims 1-10 and 13-25 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-10, 13-21, 25-29 and 41 of Application No. 11/818,927. In particular, the Examiner states that the claimed subject matter is fully disclosed in the

application and would be covered by any patent granted on that application since both applications claim common subject matter (Office Action, page 13). This rejection is respectfully traversed.

Application No. 11/818,927 has matured into the U.S. Patent No. 7,511,072 ("the '072 patent") issued to Man *et al.* on March 31, 2009. The claims of the '072 patent recite (1R)-Cyclopropanecarboxylic acid {2-[2-carbamoyl-1-(3-ethoxy-4-methoxy-phenyl-ethyl)-**7-chloro**-3-oxo-2,3-dihydro-1H-isoindol-4-yl]-amide:



or a pharmaceutically acceptable salt thereof; and a pharmaceutical composition comprising the compound. Thus, not only the claims of the '072 patent recite a structurally distinct compound (having chloro substituent in the isoindoline ring, and no 2-methanesulfonyl), they are silent as to the claimed methods. Because the claims of the '072 patent do not disclose or suggest methods of treating MDS using the recited compounds, the subject matter of the present claims is not obvious and therefore it is patentably distinct from the claims of the '072 patent. Therefore, rejection of claims 1-10 and 13-25 over the claims of the '072 patent or Application No. 11/818,927 should be withdrawn.

US Patent No. 6,020,358

Claims 1-10 and 15-20 are rejected on the ground of nonstatutory double patenting over claims 1-15 of US Patent No. 6,020,358 (hereinafter, "the '358 patent"). In particular, the Examiner alleges that the claimed subject matter is fully disclosed in the '358 patent since the '358 patent and the instant application claim common subject matter: the sulfone selected from the group consisting of (a) a compound of the formula (Office Action, page 14). Applicant respectfully disagrees.

Claim 19 of this application, which recites the sulfone compound of the formula, has been canceled. The amended claims of this application recite the specific compounds recited in claims 13-14 that are not rejected under this double patenting. The claims of the '358 patent do not disclose or suggest the claimed methods of treating MDS using the recited compounds. Accordingly, the rejection is moot and should be withdrawn.

V. REJECTIONS UNDER 35 U.S.C.§ 103

Claims 1-10 and 15-25 are rejected under 35 U.S.C. §103 as being unpatentable over Muller *et al.* (U.S. Patent 6,020,358, "the '358 patent") and Muller *et al.* (U.S. Patent 5,658,940, "the '940 patent") in view of Raza *et al.* (*Hematology* 5(4):275-284, 2000, "Raza"); in view of Celgene Corporation Annual Report, 12/31, 2000, pp. 1-165 ("Celgene Report"); and further in view of Muller *et al.* (U.S. Patent 5,605,914, "the '914 patent") (Office Action, pages 15-17). It is alleged that the claims are obvious, because the '358 patent teaches phenylsulfone compounds of formula (I); the '940 patent teaches the use of dexamethasone for controlling TNF-α and cancer; Raza teaches treating MDS using dexamethasone; Celgene Report teaches the treatment of MDS with selective cytokine inhibitors; and the '914 patent teaches the compounds recited in claim 15. *Id.* Applicant respectfully disagrees.

First, the claims have been amended to recite the specific compounds recited in claims 13-14, which are not rejected under 35 U.S.C. §103. Claim 15-37 have been canceled. The amended claims do not recite the phenylsulfone compounds of formula (I) disclosed in the '358 patent, nor the compounds of claim 15. Thus, these rejections are moot and should be withdrawn.

Further, the cited references in combination fail to establish a *prima facie* case of obviousness. The '940 patent discloses that the certain compounds are used to inhibit the actions of TNF-α (*e.g.*, columns 3-4). However, the '940 patent does not teach or suggest any uses of the specific compounds for treating patients with MDS, not to mention the specific dosing regimens or cyclic administrations recited in claims 38-50.

Raza *et al.* is also silent as to the claimed methods of the specific compounds in treating MDS. Raza *et al.* does not disclose or suggest anything about the use of the compounds recited in the instant claims for treating MDS. Indeed, Raza *et al.* discloses the use of pentoxifylline, ciprofloxacin and dexamethasone (PCD) in MDS patients and concludes that the PCD therapy showed hematologic improvement. Thus, Raza *et al.* teaches away from the claimed invention by not disclosing the use of the compounds of the instant claims, but focusing only on the use of different agents. For purpose of obviousness analysis, a prior art that teaches away negates an obviousness rejection. "[A]n applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). (Emphasis added.)

Celgene Report and the '914 patent also fail to teach or suggest any uses of the recited compounds for treating patients with MDS, much less the specific dosing regimens or cyclic administrations recited in claims 38-50.

Further, the combined teachings of the cited references do not provide the legally required reasonable expectation of success. The Patent Office has not presented evidence to demonstrate that the specific compounds of the claimed methods would be effective in treating MDS. Without such evidence, no reasonable expectation of success exists because a reasonable expectation of success requires more than a motivation to simply "vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result...." *Medichem v. Robaldo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (*quoting In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988); *see also KSR Int'l Co. v. Teleflex Inc.* 127 S.Ct. 1727, 1739 and 1742 (2007) (an obviousness determination takes into account whether the combination of elements would yield "anticipated success" or "predictable results"). Furthermore, the courts have long recognized the unpredictability of the biological properties of chemical compounds. *See, e.g., In re Eli Lilly & Co.*, 902 F.2d. 943, 948 (Fed. Cir. 1990) ("we recognize and give weight to the unpredictability of biological properties...").

Accordingly, even considering the cited references in combination, one of ordinary skill in the art would not expect that the specific compounds not disclosed nor suggested in the cited references would be useful in treating MDS. Without more specific guidance in the art, no reasonable expectation exists to the instant methods for treating MDS using the specific compounds, much less the specific dosing regimens or cyclic administrations as recited in claims 38-50. Because the Patent Office has not presented sufficient evidence of a reasonable expectation of success, a *prima facie* case of obviousness has not been made. Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

No fee, other than an extension of time fee for one month, is believed due. However, if the Examiner determines that any other fee is due, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: June 26, 2009

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